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COVID-19 Genetic Risk Variant Inherited From Neanderthals Protects Against HIV

A COVID-19 risk variant inherited from Neanderthals reduces a person's risk of contracting HIV by 27 percent.

Some people become seriously ill when infected with SARS-CoV-2 while others have only mild symptoms or no symptoms at all. In addition to risk factors such as advanced age and chronic diseases, like diabetes, our genetic heritage also contributes to our individual COVID-19 severity risk.

In the autumn of 2020, Hugo Zeberg at Karolinska Institutet and MPI-EVA and Svante Pääbo at MPI-EVA showed that we inherited the major genetic risk factor for severe COVID-19 from Neanderthals. In the spring of 2021, the same researcher duo studied this variant in ancient human DNA and observed that its frequency has increased significantly since the last ice age. In fact, it has become unexpectedly common for a genetic variant inherited from Neanderthals. Hence, it may have had a favorable impact on its carriers in the past. "This major genetic risk factor for COVID-19 is so common that I started wondering whether it might actually be good for something, such as providing protection against another infectious disease," says Hugo Zeberg, who is the sole author of the new study in *PNAS*.

The genetic risk factor is located in a region on chromosome 3 that consists of many genes. There are several genes in its vicinity that encode receptors in the immune system. One of these receptors – CCR5 – is used by the HIV virus to infect white blood cells. Zeberg found that people who carried the risk factor for COVID-19 had fewer CCR5 receptors. This led him to test whether they also had a lower risk of becoming infected with HIV. By analyzing patient data from three major biobanks (FinnGen, UK Biobank and Michigan Genomic Initiative) he found that carriers of the risk variant for COVID-19 had a 27 percent lower risk of contracting HIV. "This shows how a genetic variant can be both good and bad news: Bad news if a person contracts COVID-19, good news because it offers protection against getting infected with HIV," says Zeberg.

However, since HIV only arose during the 20th century, protection against this infectious disease cannot explain why the genetic risk variant for COVID-19 became so common among humans as early as 10,000 years ago. "Now we know that this risk variant for COVID-19 provides protection against HIV. But it was probably protection against yet another disease that increased its frequency after the last ice age," Zeberg concludes.

Reference: "The major genetic risk factor for severe COVID-19 is associated with protection against HIV" 21 February 2022, Proceedings of the National Academy of Sciences.DOI: 10.1073/pnas.2116435119

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https://bit.ly/33OxIDH

Ticks survive for 27 years in entomologist's lab

Lived for a total of 27 years but also healthily reproduced

Food is necessary for survival, but an East African species of ticks adapted to survive without feeding for eight years. Not only did they live for a total of 27 years, but they healthily reproduced long after the last male tick died.

Julian Shepherd, associate professor of biological sciences, discovered the longevity and reproduction abilities of the Argas brumpti after running out of a suitable food source for the species. He received the ticks as a gift in 1976 and decided to observe them in his lab in a habitat with stable conditions. Little did he know the original group of ticks would survive until the next century, with offspring alive and reproducing today.

The more commonly known species of ticks have a hard plate in their skin, but Argas brumpti have soft and leathery skins. Besides

their shells, the biggest difference between the two are their eating patterns. A. brumpti ticks bloat less, eat faster and eat more frequently. When Shepherd no longer had lab rabbits, mice and rats for the ticks to feed on, the A. brumpti's ability to survive with longer breaks in between meals turned out to be more significant than he first realized.

After 45 years of researching the ticks, Shepherd published his findings in the *Journal of Medical Entomology*. In the paper, "Record Longevity and Reproduction of an African Tick, Argas brumpti," Shepherd observed the record adaptability and survival of the tick.

"I am always enthralled by the adaptations of organisms to their environment—in this case, a dry environment with virtually no access to water for long periods of time and a lifestyle that must wait for very long intervals of no food between encounters with host animals," Shepherd said.

Shepherd was originally given six adult females, four adult males and three nymphs of the species. The ticks fed on the lab's rabbits, mice and rats until 1984, when Shepherd decided to stop using the animals and no longer had an available food source.

The ticks, however, survived without feeding until the last original male tick died four years later, but the females continued to live for another four years. Shepherd then reintroduced feeding to the female ticks and discovered another surprising attribute of A. brumpti.

At least one of the original females reproduced and laid a batch of eggs. Asexual reproduction in ticks is rare, which means the species can store viable sperm for long durations of time. This longevity and long-term storage of sperm is a record compared to any other tick species.

The batch of eggs contained male and female offspring, which are still alive in 2022. Further research could be conducted on these offspring to discover more information about A. brumpti's survivability and ability to conserve water and energy. These findings could be extended beyond the ticks in Shepherd's lab.

"Research on how organisms master such challenges can inform understanding of how other organisms, including us, might manage similar challenges," Shepherd said.

However, Shepherd's time with the species has come to an end. The ticks are now being sent to scientists in South Africa for further research. "I have more ideas for work with ticks, but I am now concentrating on a separate line of research working with moths on the physiology of sperm," Shepherd said. "I was very glad that the South African researchers could use the ticks."

More information: *Julian G Shepherd et al, Record Longevity and Reproduction of an African Tick, Argas brumpti (Ixodida: Argasidae), Journal of Medical Entomology (2021). DOI: 10.1093/jme/tjab205*

https://go.nature.com/3sn9ERA

Fourth dose of COVID vaccine offers only slight boost against Omicron infection

Israeli trial shows a fourth vaccination raises antibody levels but provides little extra protection against SARS-CoV-2 infection.

Smriti Mallapaty

A fourth dose of a COVID-19 vaccine restores antibodies to levels observed after the third dose but provides only a modest boost in protection against infection, according to a small trial carried out in Israel[1].

The study, posted on the medRxiv preprint server on 15 February without peer review, suggests that current mRNA vaccines hit a “ceiling of immunity” after the third dose, says Miles Davenport, a computational immunologist at the University of New South Wales in Sydney, Australia. Further doses will probably only recover the immunity lost over time owing to waning, he says.

“The third dose is really, really important,” says Gili Regev-

Yochay, a physician and infectious-diseases researcher at Sheba Medical Center in Ramat Gan, who co-authored the study. But "people who are young and healthy and don't have risk factors will probably not benefit much from a fourth dose" when faced with Omicron, she says.

Still, she and others say the fourth dose could be beneficial for people at higher risk of severe illness. Several countries, including Israel, Chile and Sweden, are offering fourth doses to older adults and other groups.

Starting in late 2021, Regev-Yochay and her colleagues enrolled 274 health-care workers in a clinical trial, in which they were given their fourth shot of an mRNA vaccine at least four months after their third. Some received the vaccine made by New York-based Pfizer with BioNTech in Mainz, Germany; others received that made by Moderna, based in Cambridge, Massachusetts.

Regardless of the vaccine brand, the fourth dose raised participants' levels of 'neutralizing' antibodies, which can block viral infection of cells. But levels after the fourth dose did not surpass those observed shortly after the third dose, suggesting that the vaccines had hit an upper limit. "You can't keep boosting antibody responses forever," says Davenport.

Omicron challenge

The researchers also assessed the neutralizing antibodies from 25 participants for the antibodies' power against several SARS-CoV-2 variants. They found that, after the third vaccine dose, participants' antibodies could block Omicron from infecting cells — but not as well as they blocked the Delta variant. After the fourth dose, the antibodies' potency against Omicron rose but also not more than their potency against Delta.

Those antibody data might explain why the fourth dose did not translate into substantial extra protection against infection with Omicron. A four-dose course of the Pfizer vaccine was 30% more protective against infection than a three-dose course; for Moderna, that extra efficacy was 11%.

That meant that, by the end of January, 52 participants who had received a fourth dose had tested positive for SARS-CoV-2 and 73 of the matched controls who had received only three doses had done so. Most of the infections were mild, and none of the participants in either the control group or the four-dose group developed severe COVID-19.

The relatively small increase in efficacy between the third and fourth doses is probably because protection offered by three doses is "already quite high", says Davenport. Both vaccines offered slightly more protection against symptomatic disease than against infection.

Chasing boosters

Ran Balicer, a public-health physician at the Clalit Health Institute in Tel Aviv, notes that the trial's efficacy estimates are based on a small sample size and have wide margins of uncertainty. Other observational studies[2] from Israel have shown higher levels of protection against infection and severe disease. "This additional protection could make a large difference for high-risk groups during a surge," says Balicer.

Ultimately, the study points to the need for new vaccines that can prevent infection with emerging variants, say researchers. The findings also highlight the importance of clarifying the optimal number of doses and time between doses for existing vaccines, says Gagandeep Kang, a virologist at the Christian Medical College in Vellore, India. "I don't think chasing an ever-increasing number of doses is going to be the solution for Omicron or future variants."

doi: https://doi.org/10.1038/d41586-022-00486-9

References *1 Regev-Yochay, G. et al. Preprint at medRxiv https://doi.org/10.1101/2022.02.15.22270948 (2022).*
2 Bar-On, Y. M. et al. Preprint at medRxiv https://doi.org/10.1101/2022.02.01.22270232 (2022). *Download references*

https://bit.ly/35vM2kM

Depression and Alzheimer's Disease Share Common Genetic Roots

Depression found to play a causal role in AD development

Epidemiological data have long linked depression with Alzheimer's disease (AD), a neurodegenerative disease characterized by progressive dementia that affects nearly 6 million Americans. Now, a new study identifies common genetic factors in both depression and AD. Importantly, the researchers found that depression played a causal role in AD development, and those with worse depression experienced a faster decline in memory. The study appears in *Biological Psychiatry*, published by Elsevier.

Co-senior author Aliza Wingo, MD, of Emory University School of Medicine, Atlanta, USA, said of the work, "It raises the possibility that there are genes that contribute to both illnesses. While the shared genetic basis is small, the findings suggest a potential causal role of depression on dementia."

The authors performed a genome-wide association study (GWAS), a technique that scans the entire genome for areas of commonality associated with particular conditions. The GWAS identified 28 brain proteins and 75 transcripts – the messages that encode proteins – that were associated with depression. Among those, 46 transcripts and 7 proteins were also associated with symptoms of AD. The data suggest a shared genetic basis for the two diseases, which may drive the increased risk for AD associated with depression.

Although previous studies had examined AD and depression using GWAS, the current work was made more powerful by using larger, newly available data sets that revealed more detailed information.

"This study reveals a relationship between depression and Alzheimer's disease and related dementia at the genetic level," said co-senior author Thomas Wingo, MD. "This is important because it may explain, at least in part, the well-established epidemiologic association between depression and higher risk for dementia."

Dr. A. Wingo added, "This relationship raises the question of whether treatment of depression can mitigate the risk for dementia. We identified genes that may explain the relationship between depression and dementia here that merit further study. Such genes may be important treatment targets for both depression and reduction of dementia risk."

"The costs of ineffectively treated depression continue to mount. There has been increasing evidence that major depressive disorder increases the risk for Alzheimer's disease, but little insight into this relationship," John Krystal, MD, Editor of *Biological Psychiatry*, said. "This innovative study, which links genetic risk mechanisms to molecular changes in the brain, provides the clearest link to date supporting the hypothesis that depression plays a causal role in the biology of Alzheimer's disease."

This does not mean that if one has an episode of depression that dementia is an inevitable result. Instead, it suggests that ineffectively treated depression may aggravate the biology of Alzheimer's disease, potentially hastening the onset of symptoms and increasing the rate of functional decline."

Reference: "Genetic Evidence Supporting a Causal Role of Depression in Alzheimer's Disease" by Nadia V. Harerimana, Yue Liu, Ekaterina S. Gerasimov, Duc Duong, Thomas G. Beach, Eric M. Reiman, Julie A. Schneider, Patricia Boyle, Adriana Lori, David A. Bennett, James J. Lah, Allan I. Levey, Nicholas T. Seyfried, Thomas S. Wingo and Aliza P. Wingo, 16 December 2021, Biological Psychiatry.
DOI: 10.1016/j.biopsych.2021.11.025

https://bit.ly/36KloFE

Largest Jurassic pterosaur on record unearthed in Scotland

It had a wingspan of at least 8 feet.

By Laura Geggel

During low tide on Scotland's Isle of Skye, a graduate student

hunting for dinosaur bones looked down at the coastal rocks and made the discovery of a lifetime: the remains of the largest pterosaur on record from the Jurassic period.

Since collecting the specimen in 2017 — an eventful excavation that involved cutting out the pterosaur chunks with diamond-tipped saws and almost losing the fossil when the tide returned — researchers have studied its anatomy and determined that it's a previously unknown species. They gave the beast the Scottish Gaelic name *Dearc sgiathanach* (jark ski-an-ach), a double meaning of "winged reptile" and "reptile from Skye," as Skye's Gaelic name (An t-Eilean Sgitheanach) means "the winged isle."

D. sgiathanach would have sported a wingspan of more than 8 feet (2.5 meters) long, a wild size for a pterosaur dating to the Jurassic period (201.3 million to 145 million years ago), the team said.

"*Dearc* is the biggest pterosaur we know from the Jurassic period, and that tells us that pterosaurs got larger much earlier than we thought, long before the Cretaceous period, when they were competing with birds — and that's hugely significant," study senior researcher Steve Brusatte, a professor and personal chair of paleontology and evolution at the University of Edinburgh, said in a statement.

The pterosaur Dearc sgiathanach flies through the Jurassic skies of what is now Scotland. **(Image credit: Natalia Jagielska)**

Pterosaurs (which are not dinosaurs) are the first known vertebrates to have evolved powered flight — a feat they accomplished about 50 million years before birds did. The oldest pterosaurs on record date to about 230 million years ago, during the Triassic period, and it was previously thought that they didn't reach huge sizes until the very late Jurassic or the Cretaceous period (145 million to 66 million years ago). For example, the largest pterosaur on record, *Quetzalcoatlus*, likely had a 36-foot-long (11 m) wingspan, meaning it was as large as a small passenger aircraft during its lifetime about 70 million years ago.

With a wingspan of more than 8 feet long, Dearc sgiathanach is largest known pterosaur from the Jurassic period. **(Image credit: Natalia Jagielska)**

However, to fly, pterosaurs needed lightweight, delicate bones — a feature that means their remains rarely fossilized well.

"To achieve flight, pterosaurs had hollow bones with thin bone walls, making their remains incredibly fragile and unfit to preserving for millions of years," study lead researcher Natalia Jagielska, a doctoral candidate of paleontology at the University of Edinburgh, said in the statement. "And yet our skeleton, about 160 million years on since its death, remains in almost pristine condition, articulated [the bones are in anatomical order] and almost complete. Its sharp fish-snatching teeth still retaining a shiny enamel cover as if he were alive mere weeks ago."

An analysis of the pterosaur's bone growth revealed that it wasn't fully grown. So, while this near-adult individual was roughly the size of today's largest flying birds, like the wandering albatross (*Diomedea exulans*), it's likely that an adult *D. sgiathanach* would have had an even longer wingspan, the researchers said. Moreover, computed tomography (CT) scans revealed that *D. sgiathanach* had large optic lobes, meaning it likely had excellent vision.

When *D. sgiathanach* was alive, the area that is now Scotland was humid and had warm waters, where the pterosaur likely fed on fish and squid with its sharp fangs and well-defined teeth, Jagielska said in a video.

The excavation of this fossil at Rubha nam Brathairean (known as

Brothers' Point) was found by Amelia Penny, a former doctoral student at in the School of GeoSciences at the University of Edinburgh who is now a research fellow in the School of Biology at the University of St Andrews in Scotland. The specimen will be added to the National Museums Scotland's collections for further study. The excavation was paid for by the National Geographic Society. The study was published online Tuesday (Feb. 22) in the journal Current Biology.

https://bit.ly/3IFN3Wt

Giant Haul of Ancient Egyptian Artifacts Spills The Lost Secrets of Mummification

A deposit of hundreds of embalming tools uncovered in Abusir, Egypt – probably the largest ever found – offers clues into a lavish funeral that likely took place about 2,600 years ago.

Marianne Guenot, Business Insider

The deposit of at least 370 ceramic jars – some of which carried heads to represent sacred animal deities – could provide unprecedented insight into the mummification process, experts told Insider.

Jars found in the Abusir embalming shaft. **(Czech Institute of Egyptology/Peter Košárek)**

"This is a really exciting and important discovery," Wojciech Ejsmond, an Egyptologist from the Warsaw Mummy Project who was not involved in the study, told Insider in an email.

"We know hundreds of mummies but our knowledge regarding the embalming process still has many gaps."

Embalming shafts or caches were commonly used in Ancient Egypt, said Miroslav Bárta, lead archaeologist on the mission and a professor of archaeology at Charles University in Prague.

He told Insider they were used to store any tool, container, or object that came into contact with the body during the 70 day-long embalming process.

The shafts of Abusir, a cemetery for ancient Egyptian elites from the neighboring city of Memphis, have been particularly rich in artifacts. Such rich caches "can be called a 'cookbook' for making mummies," Ejsmond said.

Another Abusir embalming shaft, of the tomb of Menekhibnekau, a high-ranking general, contained about 300 jars.

By comparison, the embalming cache of King Tutankhamun, a Pharaoh from the height of Egypt's ancient prosperity, only contained about a dozen, Ejsmond said.

A jar found at the Abusir site. **(Czech Institute of Egyptology/Peter Košárek)**

Menekhibnekau's embalming shaft "provided fascinating details, especially since there is no ancient text detailing the mummification process," he said. "The current discovery made by the Czech mission has great potential. As Prof. Barta said, it can elucidate the sequence of events in the embalming process."

The newly uncovered embalming shaft is about 16 ft wide and 50 ft deep. That is unusually large, per Bárta. A tomb adjoining the shaft is also vast, about 45 ft wide and more than 65 ft deep. This tomb has yet to be excavated and not much is known about the person buried there.

But because of where the tomb is and the lavishness of the embalming shaft, it is probably the resting place of one of the highest dignitaries of his time, around the 6th century BC. He was perhaps a male priest, general, or official close to the pharaoh, Bárta said.

The name "Wahibre-mery-Neith", which translates to "king beloved by the goddess Neith", was found on one of the jars, and it is "highly probable" that this was his name, said Ladislav Bareš, an

archaeologist on the dig and professor of Egyptology, also from the Charles University.

This display of wealth and over-the-top devotion seen in Abusir might have to do with the tense political situation at the time in Egypt, per Bárta. "This particular cemetery of shafts in Abusir is a wonderful example of a collapsing society that is desperate for finding new means to prevent their collapse," he said.

At around the 6th century BC, Egypt civilization was in decline. Nearby Greeks, Persians, and Nubians were looking to take over, threatening the Egyptian way of life.

This coincided with a revival of ancient sacred rites, including the recreation of elaborate historic funerals and the return to worshipping many kinds of different sacred animals, Bárta said.

"The ancient Egyptians were doing what every culture does when it's under attack from the outside: they reach back to their roots," Bárta said. "Which of course is highly interesting anthropological behavior but in most cases fails, and it also failed in case of ancient Egyptians."

https://bit.ly/3voPHvM

Largest bacterium ever discovered has an unexpectedly complex cell

Giant microbe from a mangrove could be a missing link between single-celled organisms and the cells that make up humans

By Elizabeth Pennisi

By definition, microbes are supposed to be so small they can only be seen with a microscope. But a newly described bacterium living in Caribbean mangroves never got that memo. Its threadlike single cell is visible to the naked eye, growing up to 2 centimeters—as long as a peanut—and 5000 times bigger than many other microbes. What's more, this giant has a huge genome that's not free floating inside the cell as in other bacteria, but is instead encased in a membrane, an innovation characteristic of much more complex cells, like those in the human body.

The bacterium was unveiled in a preprint posted online last week and it has astounded some researchers who have reviewed its features. "When it comes to bacteria, I never say never, but this one for sure is pushing what we thought was the upper limit [of size] by 10-fold," says Verena Carvalho, a microbiologist at the University of Massachusetts, Amherst.

The discovery is "fantastic and eye-opening," adds Victor Nizet, a physician scientist at the University of California, San Diego, who studies infectious diseases. The oversize bacterium is bigger than fruit flies and nematodes, common lab organisms that he and others sometimes infect with much smaller bacteria for their research.

Aside from upending ideas about how big—and sophisticated—microbes can become, this bacterium "could be a missing link in the evolution of complex cells," says Kazuhiro Takemoto, a computational biologist at Kyushu Institute of Technology.

A new bacterium's single-cell filaments are visible next to a dime.

Researchers have long divided life into two groups: prokaryotes, which include bacteria and single-cell microbes called archaea, and eukaryotes, which include everything from yeast to most forms of multicellular life, including humans. Prokaryotes have free-floating DNA, whereas eukaryotes package their DNA in a nucleus. Eukaryotes also compartmentalize various cell functions into vesicles called organelles and can move molecules from one compartment to another—something prokaryotes can't.

But the newly discovered microbe blurs the line between prokaryotes and eukaryotes. About 10 years ago, Olivier Gros, a marine biologist at the University of the French Antilles, Pointe-à-Pitre, came across the strange organism growing as thin filaments

on the surfaces of decaying mangrove leaves in a local swamp. Not until 5 years later did he and his colleagues realize the organisms were actually bacteria. And they didn't appreciate how special the microbes were until more recently, when Gros's graduate student Jean-Marie Volland took up the challenge of trying to characterize them.

Some microbes, such as slime molds and blue-green algae, form visible stalks or filaments composed of stacks of cells, but the group used a variety of microscopy and staining methods to verify the mangrove filaments were each just one cell. This "was something we didn't believe … at first," recalls Volland, now a marine biologist at Lawrence Berkeley National Laboratory.

Furthermore, that cell includes two membrane sacs, one of which contains all the cell's DNA, Volland and colleagues report in their 18 February preprint on bioRxiv. Volland calls that sac an organelle and that's "a big new step" that implies the two branches of life are not as different as previously thought, Carvalho says. "Perhaps it's time to rethink our definition of eukaryote and prokaryote!" agrees Petra Levin, a microbiologist at Washington University in St Louis. "It's a supercool story."

The other, water-filled sac may be the reason the bacterium could grow so big. Microbiologists used to think bacteria had to be small, in part because they eat, breathe, and get rid of toxins by diffusion of molecules through their cell's interior and there are limits to how great a distance these molecules can travel. Then in 1999, researchers discovered a giant sulfur-eating microbe roughly the size of a poppy seed off Namibia's coast. It can be big because its cellular contents are squished up against its outer cell wall by a giant water- and nitrate-filled sac. The bacteria's essential molecules can still diffuse in and out because "only [along the edge] is the cell living," says Carvalho, who worked on this group of bacteria. Scientists have since found other large sulfur-eating bacteria, but their long filaments consist of multiple cells.

Like the microbe found in Namibia, the new mangrove bacterium also has a huge sac—presumably of water—that takes up 73% of its total volume. That similarity and a genetic analysis led the research team to place it in the same genus as most of the other microbial giants and propose calling it *Thiomargarita magnifica*.

"What an excellent name!" says Andrew Steen, a bioinformatician at the University of Tennessee, Knoxville, who studies how microorganisms affect geochemical cycles. "Reading about it makes me feel exactly the same way as when I hear about an enormous dinosaur, or some celestial structure that is impossibly large or hot or cold or dense or weird in some way."

The largest *T. magnifica* cell Volland found was 2 centimeters tall, but Carvalho thinks that if not trampled, eaten, blown by wind, or washed away by a wave, they could grow even bigger.

The DNA-filled sac, also squished along the inner edge of this bacterium, proved extraordinary as well. When researchers at the Department of Energy Joint Genome Institute sequenced the DNA inside, they found the genome was huge, with 11 million bases harboring some 11,000 clearly distinguishable genes. Typically, bacterial genomes average about 4 million bases and about 3900 genes.

By labeling the DNA with fluorescent tags, Volland determined the bacterium's genome was so big because there are more than 500,000 copies of the same stretches of DNA. Protein production factories called ribosomes were inside the DNA-filled sac as well, likely making the translation of a gene's code into a protein more efficient. "Separating genetic material from everything else allows more sophisticated control and greater complexity," says Chris Greening, a microbiologist at Monash University, Clayton.

"All too often, bacteria are thought of as small, simple, 'unevolved' life forms—so-called 'bags of proteins,'" Greening adds. "But this

bacterium shows this couldn't be much further from the truth."

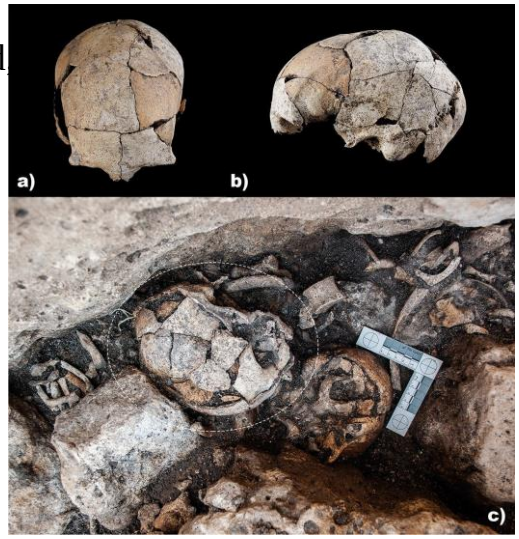
https://bit.ly/3hEfrwh

Earliest evidence of ear surgery 5,300 years ago

Skull bore evidence of a type of cranial surgery meant to cure an ear ailment.

by Bob Yirka, Phys.org

A team of several researchers from the University of Valladolid in Spain and one from the Spanish National Research Council in Italy, has found evidence of the earliest ear surgery performed on a human being. In their paper published in the journal *Scientific Reports*, the group describes their study of a human skull found at the Dolmen of El Pendónis back in 2018 and what they learned from it.



Skull under study found at El Pendón site. Superior: Frontal and lateral view of the skull (Photo: ÑFotógrafos Photography Study). Inferior: Skull with mastoidectomy in situ in the context of the megalithic ossuary. **Credit: Scientific Reports (2022). DOI: 10.1038/s41598-022-06223-6**

Dolmen of El Pendónis is a dig site near Burgos, Spain. Prior research has shown that the site was once used by early people as a funerary chamber. Prior research has also shown that the site was used for approximately 800 years, between 3,800 and 3,000 BC.

In the summer of 2018, a skull was found at the site and was put into storage. More recently, the researchers with this new effort retrieved the skull and took a closer look at it. In so doing, they found it bore evidence of a type of cranial surgery meant to cure an ear ailment. They also found evidence showing that the patient, a woman between the ages of 35 and 50, had survived the surgery—at least for a few months. There was evidence of bone regrowth in the holes that had been bored through her skull. The skull was dated to 5,300 years ago, making it the earliest known example of ear surgery.

The procedure, known today as a mastoidectomy, is done to clean out the area behind the ear that has become infected. Failure to correct the problem can lead to deafness in some cases, or progressive infections leading to more serious problems, including death. The woman who underwent the procedure required it on both ears. It is presumed that her condition was painful, enough so that she was willing to undergo what must have been an incredibly painful surgery. Further inspection of the skull showed she had lost a lot of teeth, suggesting she was quite old for the time. The researchers also found evidence of enlarged auditory canals, likely the result of the surgical procedure.

In the same tomb as the surgical patient, a flint tool was discovered—it had evidence of having been reheated several times, likely making it a cautery tool for stopping bleeding.

More information: *Sonia Díaz-Navarro et al, The first otologic surgery in a skull from El Pendón site (Reinoso, Northern Spain), Scientific Reports (2022). DOI: 10.1038/s41598-022-06223-6*

https://bit.ly/35EBOio

Branch-Like Projections Called Dendrites May Help Neurons Perform Complicated Calculations

Different types of these branch-like projections process incoming information in different ways before sending it to the body of the neuron.

By Anne Trafton, Massachusetts Institute of Technology

Within the human brain, neurons perform complex calculations on information they receive. Researchers at MIT have now demonstrated how dendrites — branch-like extensions that protrude

from neurons — help to perform those computations.

The researchers found that within a single neuron, different types of dendrites receive input from distinct parts of the brain, and process it in different ways. These differences may help neurons to integrate a variety of inputs and generate an appropriate response, the researchers say.

In the neurons that the researchers examined in this study, it appears that this dendritic processing helps cells to take in visual information and combine it with motor feedback, in a circuit that is involved in navigation and planning movement.

"Our hypothesis is that these neurons have the ability to pick out specific features and landmarks in the visual environment, and combine them with information about running speed, where I'm going, and when I'm going to start, to move toward a goal position," says Mark Harnett, an associate professor of brain and cognitive sciences, a member of MIT's McGovern Institute for Brain Research, and the senior author of the study.

Mathieu Lafourcade, a former MIT postdoc, is the lead author of the paper, which was published on February 17, 2022, in *Neuron*.

Complex calculations

Any given neuron can have dozens of dendrites, which receive synaptic input from other neurons. Neuroscientists have hypothesized that these dendrites can act as compartments that perform their own computations on incoming information before sending the results to the body of the neuron, which integrates all these signals to generate an output.

Previous research has shown that dendrites can amplify incoming signals using specialized proteins called NMDA receptors. These are voltage-sensitive neurotransmitter receptors that are dependent on the activity of other receptors called AMPA receptors. When a dendrite receives many incoming signals through AMPA receptors at the same time, the threshold to activate nearby NMDA receptors is reached, creating an extra burst of current.

This phenomenon, known as supralinearity, is believed to help neurons distinguish between inputs that arrive close together or farther apart in time or space, Harnett says.

In the new study, the MIT researchers wanted to determine whether different types of inputs are targeted specifically to different types of dendrites, and if so, how that would affect the computations performed by those neurons. They focused on a population of neurons called pyramidal cells, the principal output neurons of the cortex, which have several different types of dendrites. Basal dendrites extend below the body of the neuron, apical oblique dendrites extend from a trunk that travels up from the body, and tuft dendrites are located at the top of the trunk.

Harnett and his colleagues chose a part of the brain called the retrosplenial cortex (RSC) for their studies because it is a good model for association cortex — the type of brain cortex used for complex functions such as planning, communication, and social cognition. The RSC integrates information from many parts of the brain to guide navigation, and pyramidal neurons play a key role in that function.

In a study of mice, the researchers first showed that three different types of input come into pyramidal neurons of the RSC: from the visual cortex into basal dendrites, from the motor cortex into apical oblique dendrites, and from the lateral nuclei of the thalamus, a visual processing area, into tuft dendrites.

"Until now, there hasn't been much mapping of what inputs are going to those dendrites," Harnett says. "We found that there are some sophisticated wiring rules here, with different inputs going to different dendrites."

A range of responses

The researchers then measured electrical activity in each of those compartments. They expected that NMDA receptors would show

supralinear activity, because this behavior has been demonstrated before in dendrites of pyramidal neurons in both the primary sensory cortex and the hippocampus.

In the basal dendrites, the researchers saw just what they expected: Input coming from the visual cortex provoked supralinear electrical spikes, generated by NMDA receptors. However, just 50 microns away, in the apical oblique dendrites of the same cells, the researchers found no signs of supralinear activity. Instead, input to those dendrites drives a steady linear response. Those dendrites also have a much lower density of NMDA receptors.

"That was shocking, because no one's ever reported that before," Harnett says. "What that means is the apical obliques don't care about the pattern of input. Inputs can be separated in time, or together in time, and it doesn't matter. It's just a linear integrator that's telling the cell how much input it's getting, without doing any computation on it."

Those linear inputs likely represent information such as running speed or destination, Harnett says, while the visual information coming into the basal dendrites represents landmarks or other features of the environment. The supralinearity of the basal dendrites allows them to perform more sophisticated types of computation on that visual input, which the researchers hypothesize allows the RSC to flexibly adapt to changes in the visual environment.

In the tuft dendrites, which receive input from the thalamus, it appears that NMDA spikes can be generated, but not very easily. Like the apical oblique dendrites, the tuft dendrites have a low density of NMDA receptors. Harnett's lab is now studying what happens in all of these different types of dendrites as mice perform navigation tasks.

Reference: "Differential dendritic integration of long-range inputs in association cortex via subcellular changes in synaptic AMPA-to-NMDA receptor ratio" by Mathieu Lafourcade, Marie-Sophie H. van der Goes, Dimitra Vardalaki, Norma J. Brown, Jakob Voigts, Dae Hee Yun, Minyoung E. Kim, Taeyun Ku and Mark T. Harnett, 17 February 2022, Neuron. DOI: 10.1016/j.neuron.2022.01.025

The research was funded by a Boehringer Ingelheim Fonds PhD Fellowship, the National Institutes of Health, the James W. and Patricia T. Poitras Fund, the Klingenstein-Simons Fellowship Program, a Vallee Scholar Award, and a McKnight Scholar Award.

https://wb.md/3HsfDsE

Can Caring for a Pet Protect the Aging Brain?

Years spent caring for a dog or cat may help mitigate cognitive decline among older adults, new research suggests.

Megan Brooks

In a large study of Medicare beneficiaries, pet owners had slower cognitive decline over 6 years than their peers who did not care for a pet.

"Previous research has studied the impact of pets on overall health, mood, and quality of life; but to our knowledge, our study is the first to consider the effect of duration of pet ownership on cognitive health in older adults age 65 and older," lead author Jennifer W. Applebaum, sociology PhD candidate and NIH predoctoral fellow at University of Florida, Gainesville, told *Medscape Medical News*.

Although the study could not prove a cause-and-effect relationship, the findings do provide early evidence suggesting that long-term pet ownership may protect against cognitive decline, added senior author Tiffany J. Braley, MD, associate professor of neurology, University of Michigan, Ann Arbor.

This is "a necessary step to understanding how relationships with companion animals may contribute to brain health," Braley said.

The findings will be presented at the American Academy of Neurology (AAN) 2022 Annual Meeting in April.

Benefits to Long-Term Ownership

The researchers examined associations between pet ownership and long-term cognitive outcomes among 1369 adults participating in the Health and Retirement Study (HRS), a nationally representative cohort of US adults age 50 and older.

They used cognitive assessments from 2010 to 2016 to create a composite score derived from immediate and delayed 10-noun free recall test, serial seven subtraction test, and a backwards count test with a composite score range of zero to 27. All participants had normal cognition at baseline.

More than half of participants (53%) owned pets and 32% were long-term pet owners, caring for the pet for 5 years or more.

Compared with nonpet owners, pet owners were less apt to have hypertension (44% vs 49%) but more apt to have depression (24% vs 14%). Pet owners also had higher socioeconomic status.

Over 6 years, cognitive scores declined at a slower rate among the pet owners, and particularly among the long-term pet owners.

Taking into account other factors known to affect cognitive function, long-term pet owners, on average, had a cognitive composite score that was 1.2 points higher across 6 years than nonpet owners.

The cognitive benefits associated with longer pet ownership were more prominent for Black adults, college-educated adults, and men.

Less Stress, More Movement?

However, Braley cautioned that it is not possible to assign "clinical meaningfulness to these particular cognitive scores that are delivered through the HRS, at least not in a manner that maps back to a specific clinical test or prognosis."

She also noted that more research is needed to further explore the possible reasons why owning a pet might help protect the brain.

"If a causal pathway exists between sustained pet ownership and cognitive health, physical activity and chronic stress reduction could each be mechanisms for this relationship," she said.

"Physical activity, which is associated with dog ownership, may provide cognitive as well as physical health benefits. Prior research has also identified associations between interactions with companion animals and physiological measures of stress reduction, including reductions in cortisol levels and blood pressure, which in the long term could have an impact on cognitive health," Braley said.

Importantly, Applebaum added, "we do not recommend pet ownership as a therapeutic intervention. However, we do recommend that people who own pets be supported in keeping them, via public policy and community partnerships."

"An unwanted separation from a pet can be devastating for a bonded owner, and marginalized populations are most at-risk of these unwanted outcomes," Applebaum said.

She noted that options to help include regulating or abolishing pet fees on rental housing, particularly in low-income communities and communities of color; providing foster or boarding support for individuals who are unexpectedly unavailable to care for their pets because of a health crisis or other emergency; and free or low-cost veterinary care for low-income owners.

"Pet ownership should not be sought as a means to preserve cognitive health. However, if a causal relationship exists between pet ownership and cognitive health, such data would provide further support for the development of programs to support older adults who are interested in maintaining or initiating pet ownership," Braley added.

First Large-Scale Study

Commenting on the study for *Medscape Medical News*, Shaheen E. Lakhan, MD, PhD, a neurologist in Boston, Massachusetts, noted that this is one of the first large-scale association studies that links pet ownership and cognitive health.

"The study supports other lines of research that found mental and emotional health improvements with pets. It supports this larger narrative that caring for a pet actually improves brain health: behavioral, cognitive, emotional, and physical domains," said Lakhan, who was not involved with the research.

American Academy of Neurology (AAN) 2022 Annual Meeting. Abstract 671. To be presented April 2, 2022.

The study was supported by the National Institutes of Health, the National Heart, Lung, and Blood Institute, and the National Institute on Aging. The investigators and Lakhan have reported no relevant financial relationships.

https://bit.ly/3pmLogu

Scientists Built a Coronavirus From Scratch, Then Saw It Trying to Hide

If you want to truly understand what makes a machine tick, you need to tinker. Swap gears, lock a lever, loosen a spring, and watch how it goes.

Mike McRae

When the machine is a deadly virus, you can't afford to be so cavalier with its molecular clockwork. But researchers are getting around this problem by making minimalist versions of dangerous microbes that barely teeter on the edge of functionality.

Using this method for SARS-CoV-2 – the pathogen behind the ongoing coronavirus pandemic – has revealed a surprising way the virus's spikes act as a kind of switchblade, allowing it to hide more easily from our immune system.

Researchers from across Germany and the UK came up with 'lite' versions of SARS-CoV-2 to safely analyze its infectious behavior under lab conditions.

Described as "synthetic minimal virions", the particles consist of modules created from scratch to provide insights into key features of the virus, without an ability to operate together as an infectious unit.

"Even more important for us, as we build these synthetic virions from scratch, is that we can precisely design their composition and structure", says biologist Oskar Staufer, formerly from the Max Planck Institute for Medical Research and currently working at the University of Oxford.

"This allows us to perform a very systematic, step-by-step study on distinct mechanisms."

The first mechanism the team turned their attention to was the eponymous corona (crown) of spikes jutting from the virus's coat.

Ever since the outbreak exploded onto the world stage in early 2020, virologists have sought to understand just how these projections helps the pathogen in its quest to survive and reproduce.

It's become increasingly clear the proteins are both a help and a hindrance for the tiny invader.

Going in its favor, the spikes act like a key for a type of cellular lock called an ACE2 receptor, tricking tissues into permitting the virus entry.

Yet the proteins are also an easily identifiable feature for antibodies to latch onto and trigger a clean-out. We even base vaccines on its prominence, providing naïve, uninfected immune systems with an impression of its structure to better prepare them for an actual infection.

It turns out, the crafty coronavirus has learned a thing or two in its time that helps it get around this inconvenience.

The researchers focused on the way specific fatty acid-type immune molecules interact with the spikes in order to generate inflammation. Prior research had already highlighted a section of the spike the immune molecules stuck to. Given this region was stubbornly resistant to change, it's fair to assume it must be a pretty important structure for the virus's survival.

Now we know why. The researchers noticed the spike underwent a structural change when the immune molecule grabbed on, effectively folding itself away.

This makes it much harder to break into any nearby cells. But while in this configuration, it's also harder for the virus to attract antibodies.

"By 'ducking down' ... the spike protein upon binding of inflammatory fatty acids, the virus becomes less visible to the

immune system," says Staufer.

"This could be a mechanism to avoid detection by the host and a strong immune response for a longer period of time and increase total infection efficiency."

It's an insight into a devastating virus that continues to surprise us, and a preview of how synthetic models like this might give us the edge in limiting the pathogen's long-term impact on populations around the globe.

This research was published in *Nature Communications*.

https://bit.ly/36CpqQa

New Research Finds Words Are Needed To Think About Numbers

Among adults who vary in their knowledge of number words, the ability to reason about numbers is bound by the highest number they can count to.

By Anne Trafton, Massachusetts Institute of Technology

Among many of the Tsimane' people, who live in a remote region of the Bolivian rainforest, numbers do not play an important role in their lives, and people living in this society vary widely in how high they can count.

A new study from MIT and the University of California at Berkeley has found a relationship between the counting ability of Tsimane' individuals and their success at matching tasks that involve numbers up to about 25. The researchers found that most subjects could accurately perform tasks that require matching numbers of objects, but only up to the highest number that they could count to.

The results suggest that in order to represent an exact quantity larger than four, people may need to have a word for that number, says Edward Gibson, an MIT professor of brain and cognitive sciences.

"This finding provides the clearest evidence to date that number words play a functional role in people's ability to represent exact quantities larger than four, and supports the broader claim that language can enable new conceptual abilities," says Gibson, one of the authors of the new study.

Berkeley postdoc Benjamin Pitt is the lead author of the paper, which was published on February 8, 2022, in *Psychological Science*. Steven Piantadosi, an assistant professor of psychology at Berkeley, is the senior author of the study.

Words count

The Tsimane' are a farming and foraging society of about 13,000 people in the Amazonian rainforest. Most Tsimane' children start going to school around age 5, but education levels and counting ability vary considerably. The Tsimane' language has words for numbers up to 100, and words for numbers larger than that are borrowed from Spanish.

In a 2014 study, Gibson, Piantadosi, and former MIT graduate student Julian Jara-Ettinger found that Tsimane' children learn the meanings of number words along the same developmental trajectory as children in industrialized societies. That is, first they understand "one," then they add "two, "three," and "four," in sequence. At that point, however, a dramatic shift in understanding takes place, and children grasp the meanings of not only "five" and "six," but all of the number words they know.

Children in industrialized societies, which place a much greater emphasis on numbers, begin to learn to count around age 2 and have a sophisticated understanding of numbers and counting by age 4 or 5. However, among the Tsimane', this trajectory occurs later, beginning around age 5 and ending around age 8.

For the new study, Gibson and his colleagues identified 15 Tsimane' people who could count to somewhere between six and 20, and 15 who could count to at least 40. This gave them the opportunity to compare individuals with different verbal counting abilities and to test the hypothesis that without number words,

people are unable to do exact matching tasks that require them to mentally represent numbers greater than four.

To study this question, the researchers used a task known as "orthogonal matching." In the simplest matching task, researchers would present a line of objects, such as batteries, and then ask the participants to line up an equivalent number of a different object, such as spools of thread. With orthogonal matching, the objects are presented in a horizontal line but the participants must line up the corresponding number vertically, so they can't simply match them one-to-one.

The MIT team found that the Tsimane' people were able to perform this task, but only up to just below the number they can count to. That is, someone who can count to 10 would start making mistakes when asked to match eight or nine objects, while someone who can count to 15 would start making mistakes around 13 or 14.

Number representations

The findings suggest that tasks that require manipulation of numbers can only be done using number words or other explicit systems for representing numbers, Gibson says.

"When we get to larger numbers, even just five and six, we need some way to represent that if you want to represent it exactly," he says. "It doesn't have to be words — you could use your fingers or something like that — but you need some kind of independent representation of the numbers."

In future work, Gibson hopes to further study how children learn number representations, which is easier to do with Tsimane' participants because they learn numbers at an older age than children in Western societies.

Reference: "Exact Number Concepts Are Limited to the Verbal Count Range" by Benjamin Pitt, Edward Gibson and Steven T. Piantadosi, 8 February 2022, Psychological Science. DOI: 10.1177/09567976211034502

The research was funded by the National Science Foundation and the James S. McDonnell Foundation.

https://bit.ly/36GTytL

Rapid emergence of new SARS-CoV2 variants due to the virus' ability to momentarily accelerate its evolutionary pace

New research led by the Doherty Institute has found the SARS-CoV-2 virus has the ability to momentarily accelerate its evolutionary pace, enabling variants to emerge more rapidly than other viruses.

Recently published in *Molecular Biology and Evolution*, the team, led by University of Melbourne Dr. Sebastian Duchene, an Australian Research Council DECRA Research Fellow at the Doherty Institute and lead author on the paper, found the virus that causes the disease COVID-19 is actually undergoing short-lived mutational bursts and then returning to its 'normal' rate.

Dr. Duchene explained that usually all viruses mutate at a fairly constant rate, with most taking a year or more to develop a new variant.

"However, what we were seeing with the variants of SARS-CoV-2, particularly the variants of concern, is that they have undergone many more mutations than we would expect under the normal evolutionary pace of similar coronaviruses," Dr. Duchene said. "The Delta variant, for example, emerged within just six weeks from its ancestral form."

To understand why this was occurring, Dr. Duchene's laboratory conducted computational analyses of hundreds of genome sequences from SARS-CoV-2 strains to understand the mechanisms under which variants of concern emerge, with a focus on the first four: Alpha, Beta, Gamma and Delta.

"Initially it was believed that SARS-CoV-2 must have increased its evolutionary rate in general, but actually it's the virus's ability to temporarily increase its speed which is causing the difference in

pace," Dr. Duchene said. "It's like someone pumping the accelerator on a car."

Dr. Duchene said these bursts could be driven by a number of factors including prolonged infections in individuals, strong natural selection, which is enabling the virus to favor immune escape, or increased transmissibility with unvaccinated populations allowing the virus to rapidly spread and evolve.

The discovery highlights the importance of continued genome surveillance efforts to ensure early detection of new variants.

"With this virus evolving so rapidly, early detection is paramount in enabling us to monitor and respond to the virus," said Dr. Duchene.

He also stressed the need for increased vaccination.

"Anything we can do to have less virus out there will help reduce the probability that new variants will emerge."

The team of researchers included the Doherty Institute's Dr. Ash Porter, Dr. Wytamma Wirth and University of Melbourne Masters Student John Tay.

More information: *John H Tay et al, The Emergence of SARS-CoV-2 Variants of Concern Is Driven by Acceleration of the Substitution Rate, Molecular Biology and Evolution (2022). DOI: 10.1093/molbev/msac013*

https://bit.ly/3ssE4Cj

How squid camouflage could help prevent skin cancer in humans

It wasn't the result the scientists wanted, but the disappointment was short-lived

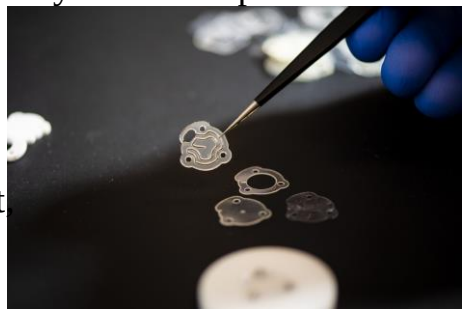
by Eva Botkin-Kowacki, Northeastern University

It wasn't the result the scientists wanted.

"When we noticed it changed color in light, we were super annoyed," says Leila Deravi, assistant professor of chemistry and chemical biology at Northeastern. That meant the substance wasn't stable enough for the applications Deravi had in mind.

But the disappointment was short-lived, as Dan Wilson, a research scientist at Northeastern's Kostas Research Institute, quickly realized that the outcome could be turned into a feature rather than a bug.

Wilson built on the unwanted chemical reaction to create dime-sized devices that change color when they've been exposed to a damaging amount of ultraviolet radiation, helping people prevent cancer-causing skin damage. The invention is essentially a tiny sticker that people could place on a shirt, hat, or bathing suit when they're headed outside.



Dan Wilson, a research scientist at Northeastern's Kostas Research Institute in Burlington, constructs a UV light sensitive detector in the Biomaterials Design Group laboratory on the Boston campus. **Credit: Alyssa Stone/Northeastern University**

"We all know more or less that too much sun on a high-UV-index day is bad. But we don't necessarily know how that translates to time in the sun," Wilson says. "This is meant to provide a visual, qualitative indication of when you may have been in the sun for too long and you should consider spending some time in the shade or reapplying your sunscreen."

The development of this device started not with humans, but with squid.

At the time, Wilson was a postdoctoral research associate in Deravi's Biomaterials Design Group. The team studies how cephalopods—tentacled sea creatures such as octopus, squid, and cuttlefish—camouflage themselves to blend into their environment. With a particular focus on squid, the researchers have identified and isolated many mechanisms, pigments, and chemical reactions that enable the animals to alter their appearances with ease.

When the circuitous discovery occurred, Wilson was testing one

substance critical to squid's color-changing capabilities: a pigment called xanthommatin. The small molecule gives squid skin its visible color.

Deravi's team had already found that xanthommatin could be manipulated to change color, and she hoped that it might be something that could be integrated into materials for a variety of applications such as apparel, or other consumer products. But in order for that to be possible, she says, xanthommatin would need to be stable and controllable in many environments.

So when Wilson noticed that xanthommatin would change color when left out on the lab bench in ambient natural light, Deravi was initially disappointed.

But Wilson saw this revelation as an opportunity. If the substance reacts to the ultraviolet radiation that is sunlight, then it could be used as a sensor for exactly that. And he had just the method in mind.

In graduate school, Wilson studied paper-based microfluidics. He leveraged that knowledge to build a system that dyes tiny pieces of paper with the xanthommatin pigment and activates it with the press of a button.

The wearable device is about the size of the tip of one of Wilson's fingers. It's made of five thin layers of carefully crafted sheets of plastic, and a round piece of paper that has been treated with the pigment and dried out. The sensor is activated when a user presses on the "button," a small reservoir of fluid in the edge of the device. That pressure pushes the fluid through channels cut into a middle layer of plastic in order to hydrate the treated paper. Once it's wet, it will react under UV radiation, changing from a yellow/orange color to a red the more it has been exposed.

The plastic itself is mostly made of the same material used for a transparent sheet for an overhead projector. There's a simple base layer, then the channel layer, topped with a layer to seal off all of the channels except for a small hole at the middle out of which the fluid flows. The fourth layer is a spacer, with a wide hole cut into it into which Wilson carefully places the paper sensor using long, thin tweezers. The sensor layer is topped with a thin film of plastic typically used in the walls or roof of a greenhouse. Wilson selected this material because it lets through as much sunlight as possible.

Wilson tested the device under many conditions, described in a paper published this month in the journal *ACS Sensors*, and calibrated it for UV levels that people are likely to experience in a range of natural conditions.

"I think you're always surprised by what a safe sun time is," he says. "It really depends on the weather, but it can be minutes."

Sunscreen, however, helps. Wilson tried coating the sensor with sunscreen and found that the color-change happened much more slowly. Users could put sunscreen on the device when they apply sunscreen to their own skin as a way to match their application with the sensor's alert, he says.

The researchers expect that people will use this device to monitor sun exposure, but the sensor also could be used in other situations where there's utility to measuring light exposure. For example, UV radiation is often used to sterilize environments. Deravi says these stickers could be used to indicate when a surface has been exposed to UV radiation for long enough to be fully sterilized.

More information: *Daniel J. Wilson et al, Wearable Light Sensors Based on Unique Features of a Natural Biochrome, ACS Sensors (2022).* *DOI: 10.1021/acssensors.1c02342*

https://bit.ly/3BVJY1O

Largest human family tree ever created retraces the history of our species

The tree is based on thousands of human genome sequences.

By Nicoletta Lanese

A new, enormous family tree for all of humanity attempts to summarize how all humans alive today relate both to one another

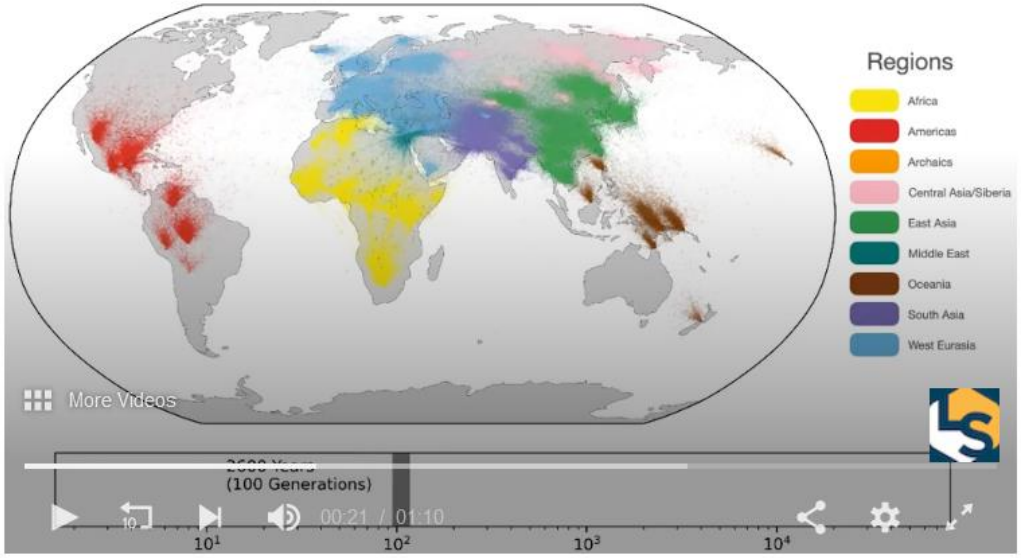
and to our ancient ancestors.

To build this family tree, or genealogy, researchers sifted through thousands of genome sequences collected from both modern and ancient humans, as well as ancient human relatives, according to a new study published Thursday (Feb. 24) in the journal Science. These genomes came from 215 populations scattered across the world. Using a computer algorithm, the team revealed distinct patterns of genetic variation within these sequences, highlighting where they matched and where they differed. Based on these patterns, the researchers drew theoretical lines of descent between the genomes and got an idea as to which gene variants, or alleles, the common ancestors of these people likely carried.

In addition to mapping out these genealogical relationships, the team approximated where in the world the common ancestors of the sequenced individuals lived. They estimated these locations based on the ages of the sampled genomes and the location where each genome was sampled.

"The way that we've estimated where ancestors live is, in particular, very preliminary," said first author Anthony Wilder Wohns, who was a doctoral student at the University of Oxford's Big Data Institute at the time of the study. Despite its limitations, the data still captured major events in human evolutionary history. For example, "we definitely see overwhelming evidence of the out-of-Africa event," meaning the initial dispersal of *Homo sapiens* from East Africa into Eurasia and beyond, said Wohns, who is now a postdoctoral researcher at the Broad Institute of MIT and Harvard.

The method the researchers used "works well to refine known ancestral locations and, as sampling improves, it has the potential to identify currently unknown human movements," Aida Andrés, an associate professor in the Genetics, Evolution and Environment Department at the University College London (UCL) Genetics Institute, and Jasmin Rees, a doctoral candidate at the UCL Genetics Institute, wrote in a commentary, also published in the journal Science on Thursday. So, in the future, when more data become available, such analyses could potentially reveal chapters of human history that are currently unknown to us.



Building the human family tree

To build a unified genealogy of humanity, the researchers first pooled genomic data from several large, publicly available data sets, including the 1000 Genomes Project, the Human Genome Diversity Project and the Simons Genome Diversity Project. From these data sets, they gathered about 3,600 high-quality genome sequences from modern-day humans; "high-quality" genome sequences are those with very few gaps or errors, which have been largely assembled in the correct order, according to a 2018 report in the journal Nature Biotechnology.

High-quality genomes from ancient humans were harder to come by, since DNA from ancient specimens tends to be severely degraded, Wohns said. However, in digging through previously published research, the team managed to find eight high-quality

ancient hominin genomes to include in their tree. These included three Neanderthal genomes, one thought to be more than 100,000 years old; a Denisovan genome roughly 74,000 to 82,000 years old; and four genomes from a nuclear family that lived in the Altai Mountains of Russia about 4,600 years ago. (Neanderthals and Denisovans are extinct relatives of *Homo sapiens*.)

In addition to these high-quality ancient genomes, the team identified more than 3,500 additional, lower-quality genomes with significant degradation, ranging from a few hundred to several thousand years old, Wohns said.

These degraded genomes did not factor into the main tree-building analysis, but the team sifted through the fragments to see which isolated alleles could be identified in the samples. This piecemeal data helped the researchers confirm when different alleles first cropped up in the genealogical record, since the specimens that the genomes came from had been radiocarbon dated.

Ancient genomes provide a "unique snapshot of genetic diversity in the past," which can help reveal when and where a genetic variant first appeared, and how it spread thereafter, Andrés and Rees told Live Science in a joint statement. "Whilst this study does not integrate the low-quality ancient genomes into the building of the tree, using them to inform the age of variants within the tree is still powerful for these means, and promises many exciting advances ahead."

Wohns and his colleagues used these data to double-check whether the lines of descent outlined in their family tree made sense, timing-wise — and, in most cases, they did.

"It's very reassuring to see that … over 90% of the time, we are being consistent with the samples that archaeologists can radiocarbon date," Wohns said. "But there are, you know, 5[%] or 10% of these genetic variants where we see discordant estimates" as to when they first appeared, according to conflicting results from the archaeological record and the estimates made by their tree-building algorithm, he noted. In these cases, the team adjusted their tree to reflect the timing that could be confirmed through radiocarbon dating, he said.

Although it's based on just a few thousand genome samples, the team's final family tree "actually captures quite a lot about the genealogy of all of humanity," Wohns said. Using the tree as a scaffold, the team then conducted their geographical analysis, to see when and where the theoretical ancestors of their sampled populations likely lived. From this, they not only found clear evidence of the out-of-Africa migration but also uncovered potential evidence of interactions between *Homo sapiens* and now-extinct hominids, such as the Denisovans, he said.

For example, their results suggested that ancestors of modern humans could be found in Papua New Guinea some 280,000 years ago, hundreds of thousands of years before the earliest known evidence of modern human habitation in the region. That doesn't necessarily suggest that *H. sapiens* actually occupied the area that long ago, "but it does perhaps suggest that there's some genetic variation that is only found in that region, and indicates that there's a really deep ancestry there that's not found elsewhere," he said.

Some of this unique ancestry may stem from modern humans breeding with Denisovans, as was also suggested in a 2019 report in the journal Cell, which found genomic evidence of modern humans interbreeding with multiple Denisovan groups.

"The trees generated in this study will undoubtedly prove useful to those studying human evolution," but the methods and data used to construct said trees are "not without their limitations," Andrés and Rees wrote in their commentary. One limitation is that most genomic sequencing has been performed in Eurasian populations, so although the new study incorporated thousands of modern

genomes, the data may not fully capture global genetic diversity, they told Live Science in an email. "Further integration of under-represented populations would continue to tackle this limitation," they said.

"There's a lot of uncertainty in these estimates," Wohns said of the team's recent results. "Unless we had the genome of everybody who ever lived, and where and when they lived, that's the only way that we can get the truth." The team reconstructed human history as closely as they could given the data at hand, but with more genome samples and more sophisticated software, the tree could definitely be refined, he said.

"The nice thing about the methods we've created is that they would work with potentially millions of samples," Wohns said. "So, as we have more data, we'll get better estimates."

Wohns said he's now working to develop new machine-learning algorithms to improve the team's estimates of where and when our ancestors lived. In a separate project, he plans to employ the same tree-building method to better understand the genetic basis of human disease. He aims to do this by pinpointing the origin point of disease-related alleles and then reconstructing how and when these gene variants spread through different populations.

The same tree-building method could also be used to trace the evolutionary history of other organisms, such as honeybees or cattle, and even infectious agents, like viruses, he added.

"The power and resolution of tree-recording methods promise to help clarify the evolutionary history of humans and other species," Andrés and Rees wrote in their commentary. "It is likely that the most powerful ways to infer evolutionary history going forward will have their foundations firmly set in these methods."

Editor's note: This article was updated at 10 a.m. on Feb. 25, 2022 with additional comments from Aida Andrés and Jasmin Rees. The original article was posted at 7 a.m. EST on the same day.

https://bit.ly/3C263vx

Researchers identify 1,044 underused plants that could combat vitamin deficiency

New research has identified more than 1,000 edible plants that could address vitamin B deficiencies for thousands of people.

In a new paper, published today in *Nature Plants*, scientists from the Royal Botanic Gardens, Kew, Imperial College London, and partners from the UK and the US, reveal the results of a study identifying 1,044 plant species that have potential to be a source of vitamin B.

Vitamin B in its various forms helps break down and release energy from food and helps maintain a healthy nervous system. It is essential for human health but is commonly deficient in both developed and developing countries.

The researchers gathered vitamin-B content data for nearly 300 plant species with known nutrition profiles. Finding that closely related species exhibit more similar nutritional values than distantly related ones, the researchers used the evolutionary relationships for these plants to predict vitamin values for over 6,000 edible plant species documented worldwide.

Their findings show approximately 1,000 plant species were newly identified as potential sources of five different B vitamins: B1, B2, B3, B5 and B9. They also discovered that 63 of the plants are threatened in their natural environment.

The future of food

Ph.D. researcher Aoife Cantwell-Jones, from the Department of Life Sciences at Imperial College London and lead author of the paper, said: "We need to pay more attention to the incredible diversity of edible plants to better understand how they can contribute to human nutrition and what we need to do to preserve them for future generations. Our study represents an important step in that direction."

A further 358 of the potential source species haven't had their conservation status assessed, so the number threatened with extinction could be much higher. Many of these vulnerable and nutritionally rich species are found in global hotspots of malnutrition such as South-East Asia and sub-Saharan Africa. These findings highlight the crucial need for further conservation action to ensure that edible plant diversity remains a reservoir of nutrition for future generations.

Dr. Samuel Pironon, Researcher in Kew's Ecosystem Stewardship Team and co-author of the paper, said: "More than two billion people suffer from malnutrition worldwide so improving long-term access to a diversity of wild and cultivated plant sources of micronutrients is key to human subsistence.

"However, very few of the thousands of edible plants found on Earth have had their nutritional contents characterized, which hinders their preservation and sustainable use. This study illustrates how our fundamental knowledge of plant diversity and evolutionary relatedness can provide tools to preserve nature and its contributions to people, including the most essential one: food."

Sources of vitamin B

The most popular current sources of B vitamins include meats such as livers, kidneys, poultry and seafood, as well as dairy products, eggs, legumes and some fresh fruits. B vitamins may also be supplemented with fortified foods, including breakfast cereals and nutritional yeast.

Some examples of non-threatened plants newly identified as potential B vitamin sources include the Digitaria genus, which is composed of many grass species of high nutritional potential, including fonio and its wild relatives that are native to the savannas of West Africa. These could represent a major food source for the future given they are also fast-growing and highly resistant to hot and dry climates.

Several oat species (Avena sp) found across Europe and the UK may represent important sources of thiamine (B1). The Ethiopian oat (Avena abyssinica) is also a traditional and underutilized food with high potential for food security.

Threatened potential sources of B vitamins include fruits and seeds of several emblematic Baobabs (Adansonia), native to Madagascar. They may be good sources of folate (B9), but are used locally for different purposes, including food but also charcoal and timber, which leads them to be "Critically Endangered." Mining and agriculture are also major threats and some species have only a handful of populations left in the wild.

Secale africanum is a wild rye only found in the Karoo in southwestern South Africa. It used to be common in the area, but it has experienced severe declines from cattle overgrazing, poor land management and diseases. Similarly, Durio kutejensis is a wild species of Durian from Borneo, Indonesia, which is threatened by deforestation and expanding agriculture.

Making the most of new sources

In order to make use of these potential source species, Aoife said: "We should first guarantee they remain available in the wild in the long term, and that we know how to make the best use of them. Both source species and traditional knowledge surrounding them should thus be prioritized for conservation."

Additionally, she said, these species should have their nutritional profiles checked using chemical methods. "They could then be used alongside other crops to diversify and complement our food systems through conventional breeding, enhancing their domestication, or directly consuming them, provided we don't over-harvest them in the wild."

More information: *Aoife Cantwell-Jones et al, Global plant diversity as a reservoir of micronutrients for humanity, Nature Plants (2022). DOI: 10.1038/s41477-022-01100-6*

https://bit.ly/3JWqL2A

Canada Approves World's First Plant-Based COVID-19 Vaccine

Canada has ordered 76 million doses of Covifenz, the main ingredient of which was manufactured in the leaves of a tobacco relative.

Natalia Mesa

On Thursday (February 25), Health Canada, the department of the Government of Canada responsible for Canada's national health policy, approved the world's first plant-based COVID-19 vaccine for use in adults aged 18 to 64. Too little data exists for approval in adults over 65, the regulators concluded.

Medicago, the Quebec-based pharmaceutical company behind the plant-based jab, has agreed to supply the Canadian government with 76 million doses of the vaccine as soon as possible, the Associated Press reports.

"We're at a stage where we're ramping up capacity to meet the supply agreement," Marc-André D'Aoust, executive vice president of innovation, development, and medical affairs at Medicago, tells Reuters.

Medicago uses *Nicotiana benthamiana*, a close relative of the tobacco plant, to manufacture virus-like particles that mimic SARS-CoV-2's spike protein but don't cause infection or disease. The particles are then harvested from the plants, purified, and combined with an immune-boosting adjuvant—made by British pharmaceutical company GlaxoSmithKline—to make the vaccine. The virus-like particles can be stored in a refrigerator at two to eight degrees celsius, unlike the mRNA vaccines that require extremely cold storage.

According to the Associated Press, Canadian officials based their decision on a study of 24,000 adults across six countries. The study found that the vaccine was 75.3 percent effective against the Delta variant of the virus, and 71 percent effective against all coronavirus variants except Omicron, which was not prevalent when the study was underway. Side effects of the vaccine were reported to be mild and included fever and fatigue. The vaccine works best when the two doses are given 21 days apart.

"We will generate Omicron-specific vaccine efficacy data soon, and in parallel we're also collecting immunogenicity data, antibody response from our vaccine against Omicron," D'Aoust tells *The Toronto Star*. D'Aoust also says that Medicago plans to test the shot as a booster.

Isaac Bogoch, an infectious diseases specialist based in Toronto, tells *CBC News* that the vaccine's approval is good news, even though most Canadians are already vaccinated with two or more doses.

"Is this going to have a major impact on us here in Canada? Probably not. But there might be some individuals who choose to get vaccinated with a non-mRNA product," he says, referring to the shots offered by Pfizer-BioNTech and Moderna.

https://bit.ly/3hrf3RE

Spectacular Chain-Mail Structure: The Protective Armor of Superbug C. difficile Revealed

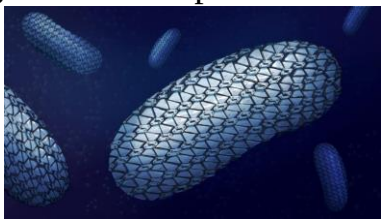
Spectacular structure of chain-mail may explain the success of C.diff at defending itself against antibiotics and immune system molecules.

The spectacular structure of the protective armor of superbug *C.difficile* has been revealed for the first time showing the close-knit yet flexible outer layer – like chain mail.

This assembly prevents molecules from getting in and provides a new target for future treatments, according to the scientists who have uncovered it.

Publishing in *Nature Communications*, the team of scientists from Newcastle, Sheffield, and Glasgow Universities together with

colleagues from Imperial College and Diamond Light Source, outline the structure of the main protein, SlpA, that forms the links of the chain mail and how they are arranged to form a pattern and create this flexible armor. This opens the possibility of designing *C. diff* specific drugs to break the protective layer and create holes to allow molecules to enter and kill the cell.



The spectacular structure of the protective armor of superbug C. difficile has been revealed for the first time showing the close-knit yet flexible outer layer – like chain mail. This assembly prevents molecules from getting in and provides a new target for future treatments, according to the scientists at Newcastle, Sheffield, and Glasgow Universities who have uncovered it.
Credit: Newcastle University, UK

Protective armor

One of the many ways that diarrhea-causing superbug *Clostridioides difficile* has to protect itself from antibiotics is a special layer that covers the cell of the whole bacteria — the surface layer or S-layer. This flexible armor protects against the entry of drugs or molecules released by our immune system to fight bacteria.

The team determined the structure of the proteins and how they arranged using a combination of X-ray and electron crystallography. Corresponding author Dr. Paula Salgado, Senior Lecturer in Macromolecular Crystallography who led the research at Newcastle University said: "I started working on this structure more than 10 years ago, it's been a long, hard journey but we got some really exciting results! Surprisingly, we found that the protein forming the outer layer, SlpA, packs very tightly, with very narrow openings that allow very few molecules to enter the cells. S-layer from other bacteria studied so far tend to have wider gaps, allowing bigger molecules to penetrate. This may explain the success of *C.diff* at defending itself against the antibiotics and immune system molecules sent to attack it.

"Excitingly, it also opens the possibility of developing drugs that target the interactions that make up the chain mail. If we break these, we can create holes that allow drugs and immune system molecules to enter the cell and kill it."

One of the current challenges in our fight against infections is the growing ability bacteria have to resist the antibiotics that we use to try to kill them. Antibiotic or more generally, antimicrobial resistance (AMR), was declared by WHO as one of the top 10 global public health threats facing humanity.

Different bacteria have different mechanisms to resist antibiotics and some have multiple ways to avoid their action – the so-called superbugs. Included in these superbugs is *C. diff*, a bacteria that infects the human gut and is resistant to all but three current drugs. Not only that, it actually becomes a problem when we take antibiotics, as the good bacteria in the gut are killed alongside those causing an infection and, as *C. diff* is resistant, it can grow and cause diseases ranging from diarrhea to death due to massive lesions in the gut. Another problem is the fact that the only way to treat *C.diff* is to take antibiotics, so we restart the cycle and many people get recurrent infections.

Determining the structure allows the possibility of designing *C. diff*-specific drugs to break the S-layer, the chainmail, and create holes to allow molecules to enter and kill the cell.

Colleagues, Dr. Rob Fagan and Professor Per Bullough at the University of Sheffield carried out the electron crystallography work.

Dr. Fagan said: "We're now looking at how our findings could be used to find new ways to treat *C. diff* infections such as using bacteriophages to attach to and kill *C. diff* cells — a promising potential alternative to traditional antibiotic drugs."

From Dr. Salgado's team at Newcastle University, PhD student

Paola Lanzoni-Mangutchi and Dr. Anna Barwinska-Sendra unraveled the structural and functional details of the building blocks and determined the overall X-ray crystal structure of SlpA. Paola said: "This has been a challenging project and we spent many hours together, culturing the *diff*icult bug and collecting X-ray data at the Diamond Light Source synchrotron."

Dr. Barwinska-Sendra added: "Working together was key to our success, it is very exciting to be part of this team and to be able to finally share our work."

The work is illustrated in the stunning image by Newcastle-based science Artist and Science Communicator, Dr. Lizah van der Aart.

Reference: "Structure 1 and assembly of the S-layer in C. difficile" by Paola Lanzoni-Mangutchi, Oishik Banerji, Jason Wilson, Anna Barwinska-Sendra, Joseph A. Kirk, Filipa Vaz, Shauna O'Beirne, Arnaud Baslé, Kamel El Omari, Armin Wagner, Neil F. Fairweather, Gillian R. Douce, Per A. Bullough, Robert P. Fagan and Paula S. Salgado, 25 February 2022, Nature Communications. DOI: 10.1038/s41467-022-28196-w

https://go.nature.com/3vpMuMk

Wuhan market was epicentre of pandemic's start, studies suggest

Report authors say that the coronavirus SARS-CoV-2 jumped from animals sold at the market into people twice in late 2019 — but some scientists want more definitive evidence.

Amy Maxmen

Scientists have released three studies that reveal intriguing new clues about how the COVID-19 pandemic started. Two of the reports trace the outbreak back to a massive market that sold live animals, among other goods, in Wuhan, China[1,2], and a third suggests that the coronavirus SARS-CoV-2 spilled over from animals — possibly those sold at the market — into humans at least twice in November or December 2019[3]. Posted on 25 and 26 February, all three are preprints, and so have not been published in a peer-reviewed journal.

These analyses add weight to original suspicions that the pandemic began at the Huanan Seafood Wholesale Market, which many of the people who were infected earliest with SARS-CoV-2 had visited. The preprints contain genetic analyses of coronavirus samples collected from the market and from people infected in December 2019 and January 2020, as well as geolocation analyses connecting these samples to a section of the market where live animals were sold. Taken together, these different lines of evidence point towards the market as the source of the outbreak — much like animal markets were ground zero for the severe acute respiratory syndrome (SARS) epidemic of 2002–2004 — says Kristian Andersen, a virologist at the Scripps Research Institute in La Jolla, California, and an author on two of the reports. "This is extremely strong evidence," he says.

Still, none of the studies contain definitive evidence about what type of animal might have harbored the virus before it spread to humans. Andersen speculates that the culprits could be raccoon dogs, a squat dog-like mammal used for food and for their fur in China. One of the studies he coauthored[2] suggests that raccoon dogs were sold in a section of the market where several positive samples were collected. And reports[4] show that the animals are capable of harboring other types of coronaviruses.

Some virologists say that the new evidence pointing to the Huanan market doesn't rule out an alternative hypothesis. Namely, they say that the market could have just been the location of a massive amplifying event, in which an infected person spread the virus to many other people, rather than the place of the original spillover.

"Analysis-wise, this is excellent work, but it remains open to interpretation," says Vincent Munster, a virologist at the Rocky Mountain Laboratories, a division of the National Institutes of Health, in Hamilton, Montana. He says searching for SARS-CoV-2 and antibodies against it in blood samples collected from animals sold at the market, and from people who sold animals at the market,

could provide more definitive evidence of COVID-19's origins. The number of positive samples from the market suggests an animal source, Munster says. But he is frustrated that more thorough investigations haven't already been conducted: "We are talking about a pandemic that has upended the lives of so many people."

Ground zero?

In early January 2020, Chinese authorities identified the Huanan market as a potential source of a viral outbreak because the majority of people infected with COVID-19 at that time had been there in the days before they began to show symptoms, or were in contact with people who had. Hoping to stem the outbreak, Chinese authorities shuttered the market. Then researchers collected samples from poultry, snakes, badgers, giant salamanders, Siamese crocodiles and other animals sold there. They also swabbed drains, cages, toilets and vendor stalls in search of the pathogen. Following an investigation led by the World Health Organization (WHO), researchers released a report in March 2021 showing that all of the nearly 200 samples collected directly from animals were negative, but that more than 1,000 environmental samples from the stalls and other areas were positive.

A research team from China including the head of China's Center for Disease Control and Prevention (CDC) has now genetically sequenced those positive samples, releasing the results in a preprint posted on 25 February[1]. The scientists confirm that the samples contain SARS-CoV-2 sequences nearly identical to those that have been circulating in humans. Further, they show that the two original virus lineages circulating at the start of the pandemic, called A and B, were both present at the market.

"It's a nice piece of work," says Ray Yip, an epidemiologist who is a former director of the China branch of the US Centers for Disease Control and Prevention. "They've confirmed that the Huanan market was indeed a very important spreading location."

As soon as the report from China posted online, Andersen and his colleagues rushed to post the manuscripts they had been working on for weeks.

In one[2], the team zeroed in on the southwestern section of the Huanan market, where live animals were sold as recently as 2019, as being the potential epicentre of the outbreak. They arrived at this conclusion by compiling information on the first known COVID-19 cases in China, as reported in various places, including the WHO investigation, newspaper articles, and from audio and video recordings of doctors and patients in Wuhan. This geospatial analysis found that 156 cases in December 2019 clustered tightly around the market and then gradually became more dispersed around Wuhan in January and February 2020.

They also examined the locations of the positive samples collected in the market, as reported in the WHO study, and fleshed out information about their potential surroundings by collecting business registration information, photographs of the market before it closed, and scientific reports that have emerged since the WHO's investigation. For example, one paper published last year[5] documented some 47,000 animals — including 31 protected species — sold in Wuhan markets between 2017 and 2019.

In one major finding in the new preprint, Andersen and colleagues mapped five positive samples from the market to a single stall that sold live animals, and more specifically to a metal cage, to carts used to move animals, and to a machine used to remove bird feathers. One of the coauthors on the report, virologist Eddie Holmes at the University of Sydney in Australia, had been to this stall in 2014 and snapped photographs — included in this study — of a live raccoon dog in a metal cage, stacked above crates of poultry, with the whole assembly sitting atop sewer drains. Notably, in the study from the China CDC, sewage at the market tested

positive for SARS-CoV-2.

In a second report[3], Andersen and colleagues concluded that lineage A and lineage B of SARS-CoV-2 are too different from one another on a genetic level for one to have evolved into the other quickly in humans. Therefore, they suggest that the coronavirus must have evolved within non-human animals and that the two different lineages spread to humans separately. Because lineage B was the far more prevalent variety in January 2020, among other reasons, the authors suggest that it spilled over into humans before lineage A. Other outbreaks of coronaviruses, such as the SARS and Middle East respiratory syndrome (MERS) epidemics, also resulted from repeated introductions from wildlife, the paper notes.

Taking all of the new data together, and adding a degree of speculation, Andersen suggests that raccoon dogs could have been infected on a farm that then sold the animals at the markets in Wuhan in November or December 2019, and that the virus might have jumped to people handling them, or to buyers. At least twice, those infections could have spread from an index case to other people, he says.

'As good as it gets'

Over the past year, Michael Worobey, a virologist at the University of Arizona, in Tucson, and an author on the papers with Andersen[2,3], says that his thinking on the origins of COVID-19 has shifted. Back in May 2021, he led a letter published in *Science*[6] in which he and other researchers pressed the scientific community to keep an open mind about whether the pandemic stemmed from a laboratory, a controversial hypothesis suggesting that SARS-CoV-2 was either created in a lab, or was accidentally or intentionally released by researchers at the Wuhan Institute of Virology. "You want to take this kind of thing seriously," he explains.

But since May, additional evidence has come to light that supports a zoonotic origin story similar to that of HIV, Zika virus, Ebola virus and multiple influenza viruses, he says. "When you look at all of the evidence, it is clear that this started at the market," he says. Separate lines of analysis point to it, he says, and it's extremely improbable that two distinct lineages of SARS-CoV-2 could have been derived from a laboratory and then coincidentally ended up at the market.

Nonetheless, Munster says he is not completely convinced of two spillover events because, alternatively, the virus might have evolved from one lineage into the other within a person who was immunocompromised. He adds that more data collected from people and animals is needed to answer this question, and to show that the first spillover occurred at the Huanan market. David Relman, a microbiologist at Stanford University in California, agrees that the preprints are not definitive, and that they exclude the possibility that people were infected prior to the outbreak at the market, but went undiagnosed.

Holmes fears that additional samples from early human cases and from animals might never materialize. Last July, for example, Chinese officials said that they planned to analyse patient blood samples from 2019, stored at the Wuhan Blood Centre — but if that study has been conducted, it has yet to be made public. "This is as good as it gets," Holmes says. "What we should focus on now is trying to keep these events from happening again."

doi: https://doi.org/10.1038/d41586-022-00584-8

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https://bit.ly/36O0sxv

A Near-Real-Time View of the Drains Inside the Human Brain

A new non-invasive technique provides a near-real-time view of the human brain's waste-clearance vessels.

A joint research team at the Medical University of South Carolina (MUSC) and the University of Florida describes the first non-invasive and near real-time visualization of the human brain's waste-clearance system in *Nature Communications*. The brain is densely organized, and visualizing the structures dedicated to waste removal, also known as lymphatic structures, had been a limitation in the field.

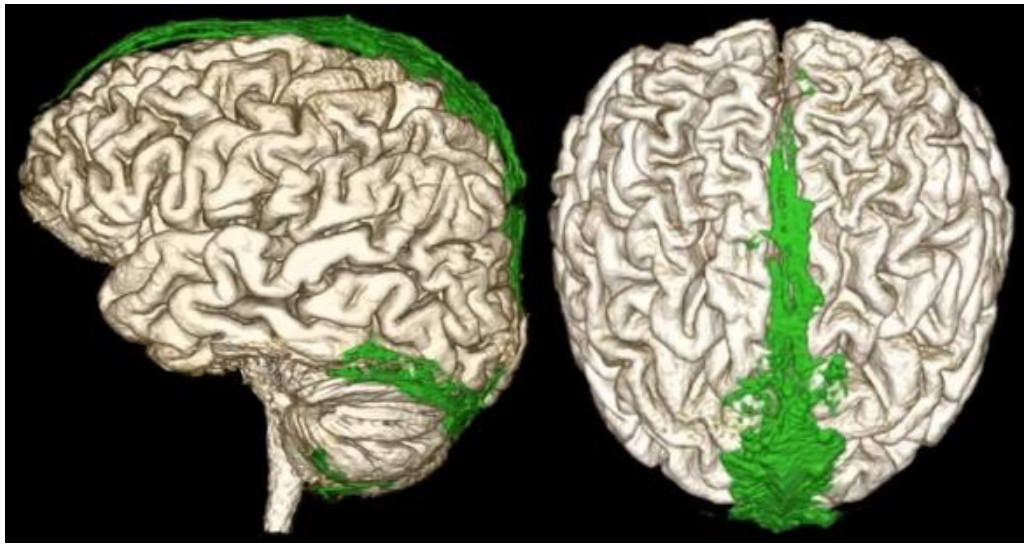
"This is the first report to show the complete human brain lymphatic system architecture in living humans," said Onder Albayram, Ph.D., an assistant professor in the Department of Pathology and Laboratory Medicine and Department of Neuroscience at MUSC, who led the research team and is senior author of the article.

Albayram was intrigued by the possibility of lymphatic structures in the brain. "The lymphatic clearance system is all over the body for different organs," he said. "I asked myself simply, 'Why not the brain?'"

Improved visualization of the brain's waste-clearance system could enhance our understanding of how the healthy brain functions. It could also provide insight into what goes wrong in neurogenerative diseases such as Alzheimer's and how the brain recovers from traumatic brain injuries (TBIs).

Pound for pound, the brain is the most metabolically demanding mass in the body – weighing around 3 pounds but requiring 20% of total oxygen consumption. That metabolic demand comes with the need to dispose of waste regularly.

As blood carrying oxygen permeates tissues to deliver vital nutrients, it collects pathogens, damaged cells, and waste. This fluid then drains into lymphatic vessels to be filtered through lymph nodes, which dispose of any unwanted waste products.



MRI showing the dorsal flow of the brain's waste-clearance system. **Credit: Dr. Onder Albayram, Medical University of South Carolina**

"It had long been believed that the brain lacked lymphatic vessels," said Sait Albayram, M.D., a professor in the Department of Neuroradiology at the University of Florida, who is the lead author of the article.

"That thinking began to change about a decade ago, as the first reports from experiments in rodents hinted at lymphatic vessels surrounding the brain, side by side with blood vessels. But evidence of lymphatic vessels in human brains remained scarce before this study."

Onder Albayram likens the brain in the skull to an apple suspended inside of a jar. Coating the inside of the "jar," or skull, is a layer of delicate membranes known as the meninges. A liquid known as cerebrospinal fluid (CSF) surrounds the brain. The conventional thinking was that waste-laden fluid from the brain flowed out into

the CSF along blood vessels, was transported out of the skull and then drained into veins. Research over the past decade has hinted instead that the process is more complex and suggested the existence of dedicated waste-removing lymphatic vessels in the brain.

However, witnessing these vessels in action in a living human brain has posed technical limitations. Chief among them is the required use of the toxic rare-earth metal, Gadolinium, a toxic rare-earth metal used as a contrast agent during MRI, a technique used to visualize and differentiate structures in the brain.

In this study, investigators were able to overcome this limitation and use MRI to visualize lymphatic vessels in the meninges without the need for contrast agent. Instead, the team used differences in the brain's own protein content to create a gradient in contrast. Structures with low protein content appear dark and those with high protein content appear light, with high enough resolution to see intricate details.

"The discovery of the meningeal lymphatic networks in mammals in the last decade opened a new chapter in our understanding of cellular waste management in the brain," said Adviye Ergul, M.D., Ph.D., a professor in the Department of Pathology and Laboratory Medicine at MUSC, who was not an author of the study.

"This novel study takes it one step further by eliminating the need to inject contrast agents to visualize the lymphatic vessels," she said. "This is a major accomplishment that will invigorate the field to go deeper into the brain and expand our knowledge of the brain lymphatic system."

This simple yet innovative approach enabled investigators to capture clear images of lymphatic vessels, with their high protein content – about 50-fold greater than that of CSF – as they connected areas within the brain to lymph nodes in the neck.

The research team then went on to compare how aged brains differ from younger ones, finding a reduction in waste clearance in older brains.

Using this non-invasive MRI technique, researchers and physicians can now actually see what the lymphatic vessels of a healthy brain look like, said Onder Albayram, and study how they change as we age. They can also determine their role in the progression of neurodegenerative diseases, such as Alzheimer's and related dementia. The technique could also be used to study ways to increase the brain's lymphatic output as we age and perhaps offer insight into recovery after TBI.

"Imagine again the brain in the jar, surrounded by delicate lymphatic vessels," said Onder Albayram. "What happens during a TBI? Are the lymphatic vessels damaged, and how do they recover? This technique will enable us to begin to answer these questions."

Reference: "Non-invasive MR imaging of human brain lymphatic networks with connections to cervical lymph nodes" by Mehmet Sait Albayram, Garrett Smith, Fatih Tufan, Ibrahim Sacit Tuna, Mehmet Bostancıklıoğlu, Michael Zile and Onder Albayram, 11 January 2022, Nature Communications. [DOI: 10.1038/s41467-021-27887-0](https://doi.org/10.1038/s41467-021-27887-0)